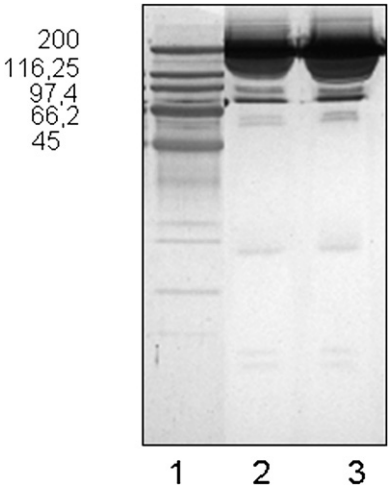

FIG 2. Natalizumab SDS-PAGE under nonreducing conditions: standard high molecular weight (Bio-Rad; *lane 1*), 20 μg of natalizumab *(lane 2)*, and 40 μg of natalizumab *(lane 3)*. One band in the high-molecular-weight range is intensely visualized.

IgG hypersensitivity reactions to natalizumab have been described previously, and IgG against natalizumab is present in up to 12% of patients receiving natalizumab.[5] Other immunologic events, such as serum sickness–like delayed hypersensitivity reactions, have also been reported.[6] IgE-mediated reactions have been described with other mAbs, such as cetuximab[7] or omalizumab.[8] Chung et al[7] observed that these patients had IgE against cetuximab before therapy. These IgE antibodies were specific for an oligosaccharide, galactose-α-1,3-galactose, which is present in the Fab portion of the cetuximab heavy chain.[6] However, this mechanism could be discarded in omalizumab hypersensitivity reactions because it is grown in a Chinese hamster ovary cell line that does not express the enzyme α-1,3-galactosyl transferase and thus has a different glycosylation pattern. A positive skin prick test response to polysorbate has been demonstrated in some patients allergic to omalizumab, but the mechanism has not been elucidated in many other cases.[8]

To our knowledge, we are describing the first case of a probable IgE-mediated hypersensitivity reaction to natalizumab diagnosed by means of an *in vitro* and *in vivo* study.

Monoclonal antibody and fusion protein therapy is rapidly increasing. Because of the complex molecular structure of immunoglobulins, a variety of heterogeneous immunologic reactions is possible. Assessing reactions to these therapies is a growing challenge to allergists.

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Infants aged 12 months can mount adequate serotype-specific IgG responses to pneumococcal polysaccharide vaccine

To the Editor:

Streptococcus pneumoniae is a major cause of bacterial pneumonia, meningitis, bacteremia, and otitis media leading to an estimated 1 million deaths per year worldwide in children younger than 5 years. The capsule of *S pneumoniae* is the major virulence

TABLE I. Serotype-specific IgG GMC before and after 23vPPV immunization in infants at 12 months of age

	Pre-23vPPV	2 Weeks post-23vPPV	
Serotype	GMC μg/mL (95% CI)	GMC μg/mL (95% CI)	*P* value*
1	0.17 (0.13-0.22)	2.04 (1.49-2.80)	<.0001
2	0.28 (0.23-0.35)	12.48 (9.66-16.12)	<.0001
3	0.37 (0.26-0.53)	13.74 (10.55-17.91)	<.0001
4	0.08 (0.06-0.10)	2.37 (1.76-3.20)	<.0001
5	0.26 (0.20-0.34)	2.77 (2.15-3.57)	<.0001
6B	0.14 (0.12-0.17)	0.31 (0.23-0.42)	<.05
7F	0.10 (0.08-0.14)	2.58 (1.98-3.37)	<.0001
8	0.26 (0.20-0.32)	13.59 (10.72-17.23)	<.0001
9N	0.12 (0.09-0.15)	3.06 (2.18-4.30)	<.0001
9V	0.09 (0.07-0.12)	1.21 (0.90-1.62)	<.0001
10A	0.20 (0.16-0.24)	0.87 (0.65-1.17)	<.0001
11A	0.10 (0.08-0.13)	2.21 (1.58-3.08)	<.0001
12F	0.06 (0.05-0.08)	0.39 (0.28-0.54)	<.0001
14	0.20 (0.16-0.25)	0.41 (0.29-0.59)	NS
15B	0.17 (0.14-0.22)	0.79 (0.59-1.05)	<.0001
17F	0.11 (0.09-0.13)	1.39 (0.98-1.97)	<.0001
18C	0.07 (0.05-0.08)	1.23 (0.88-1.72)	<.0001
19A	0.29 (0.24-0.36)	0.79 (0.55-1.12)	<.05
19F	0.47 (0.36-0.62)	1.15 (0.81-1.62)	NS
20	0.10 (0.08-0.12)	0.90 (0.61-1.34)	<.0001
22F	0.36 (0.29-0.46)	5.23 (3.47-7.88)	<.0001
23F	0.19 (0.15-0.25)	0.42 (0.30-0.57)	NS
33F	0.14 (0.11-0.17)	2.01 (1.44-2.80)	<.0001

No. of infants = 56.
NS, Not significant.
*Comparison of serotype-specific IgG before and 2 weeks after 23vPPV immunization (paired *t* test).

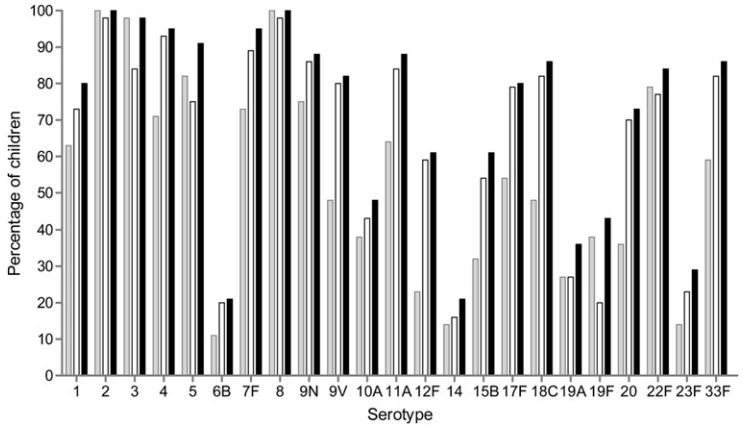

FIG 1. Proportion of infants at 1 year of age (n = 56) with an adequate serotype-specific IgG response 2 weeks after 23vPPV immunization. An adequate response is defined as a postimmunization titer ≥1.3 μg/mL and/or a 4-fold increase over baseline titer. *Gray bars* represent ≥1.3 μg/mL; *white bars* represent a 4-fold increase on baseline titer; *black bars* represent ≥1.3 μg/mL and/or a 4-fold increase on baseline titer.

factor by which pneumococci cause invasive disease. Immunity against *S pneumoniae* is mediated by phagocytosis of the organism in the presence of complement and serotype-specific antibody. Capsular polysaccharide antigens, classified as T-independent type II antigens, are considered to stimulate B-lymphocytes directly to produce antigen-specific opsonic antibody without inducing immunologic memory or affinity maturation. Polysaccharide antigens, with bound complement C3d, are recognized directly by the B lymphocyte through CD21, which associates with CD19 to enhance and prolong antigen signaling.[1] On the basis of a limited number of small studies, the ability to mount T-independent responses is considered to be absent in the neonate and poor in children younger than 2 years.[2-4] This may be a result of lower CD21 expression on neonatal and infant B cells and/or the immaturity of the splenic marginal zone.[5]

Pneumovax (Merck and Co, NJ), the 23-valent pneumococcal polysaccharide vaccine (23vPPV), contains 25 μg polysaccharide from each of 23 serotypes representing 85% to 90% of the serotypes causing invasive pneumococcal disease in the United States. Current guidelines define an adequate response to 23vPPV immunization as a 4-fold increase on preimmunization titer and/or a postimmunization titer ≥1.3 μg/mL to at least 50% of serotypes tested for children age 2 to 5 years and at least 75% of serotypes for older children and adults.[6] These guidelines are based on results from small study cohorts or studies examining a limited number of serotypes.[2-4,6] Previous studies suggest that infants 6 to 12 months of age can respond to some antigens in 23vPPV; however, these studies measured responses to only a few serotypes in a small number of subjects and used less specific older generation assay methods.[4-6] The ontogeny of the immune response to T-independent type II antigens in early life has not been formally assessed in larger groups of children.

In this study, the immunogenicity of 23vPPV was evaluated in 56 healthy Fijian infants who received 23vPPV as their primary pneumococcal vaccination at 12 months of age. Serotype-specific IgG to the 23 serotypes in the vaccine was measured by a standardized ELISA using cell wall polysaccharide and serotype 22F double absorption.[7] The geometric mean concentration (GMC) and 95% CI of serotype-specific IgG before and 2 weeks after immunization are reported in Table I. At 2 weeks post-23vPPV, a greater than 4-fold increase in IgG GMC was detected for 18 (78%) of 23 serotypes, with a 2-fold increase in IgG GMC for serotypes 6B, 19A, 19F, and 23F. There was a significant increase ($P < .05$) over baseline at 2 weeks post-23vPPV for all serotypes except 14, 19F, and 23F. This response was maintained at 5 months post-23vPPV for 13 (57%) of 23 serotypes (data not shown).

The percentage of infants achieving an adequate response (either a 4-fold increase over baseline titer or a posttiter ≥1.3 μg/mL) to each serotype is shown in Fig 1. All infants responded with a posttiter ≥1.3 μg/mL to serotypes 2 and 8. Ninety-eight percent of infants mounted an adequate response to 11 of 23 serotypes (Table II). Thirty-two infants (54%) responded to at least 17 of 23 serotypes. Two infants (4%) responded to all 23 serotypes. All infants responded to at least 9 of 23 serotypes. Serotypes 6B, 14, and 23F were the least immunogenic in this age group, with 12 infants (21%) producing an adequate response to serotypes 6B and 14, whereas 16 infants (29%) produced an adequate response to serotype 23F. Previous studies have also reported the low immunogenicity of serotypes 6B and 23F.[3]

The number and selection of serotypes to be tested are critical to the evaluation of an adequate immune response to 23vPPV. The hierarchy of responses to pneumococcal serotypes 2 weeks post-23vPPV in this population confirms that the selection of serotypes for measurement of specific IgG by laboratories is critical. If serotype-specific immune responses in this cohort were evaluated for 12 of the more immunogenic serotypes (eg, 2, 3, 4, 5, 7F, 8, 9N, 9V, 11A, 18C, 22F, and 33F), an adequate response would be detected in all infants. Conversely, if immune responses to 11 of the least immunogenic serotypes were assessed (eg, 1, 6B, 10A, 12F, 14, 15B, 17F, 19A, 19F, 20F, and 23F), 38% or 21 infants would be considered to have an inadequate response. If it is impossible to test all serotypes in the vaccine, the decision on which serotypes to assay should be based on the patient population and the serotypes causing disease in that population.

In 1998, Shann[8] suggested that a controlled trial of 23vPPV for children younger than 2 years was warranted considering the morbidity and mortality caused by *S pneumoniae* in this age group, the increasing antibiotic resistance of many of the bacterial strains, and the cost and the limited availability of pneumococcal conjugate vaccines in developing countries. We have shown 23vPPV to

TABLE II. The proportion of infants with a postimmunization titer ≥1.3 μg/mL, a 4-fold increase from baseline titer, and an adequate response 2 weeks post-23vPPV immunization against the number of serotypes to which they respond

No. of serotypes	Postimmunization titer >1.3 μg/mL	A 4-fold increase from baseline titer	Adequate response*
22	2%	5%	5%
19	5%	16%	25%
17	14%	39%	54%
14	41%	73%	82%
11	64%	89%	98%

No. of infants = 56.
*Adequate response defined as a postimmunization titer ≥1.3 μg/mL and/or a 4-fold increase from baseline titers.

be immunogenic in this age group, with all infants enrolled in the study capable of producing adequate serotype-specific IgG to at least 9 of the 23 serotypes at 12 months of age.

Nevertheless, there are several issues concerning the use of 23vPPV in children younger than 2 years that require further clarification. It will be important to monitor the kinetics of the immune response over time, because recent studies and our own data raise the possibility that early administration of full-dose 23vPPV may result in immune hyporesponsiveness to subsequent challenge with polysaccharide antigens.[9] Further investigations including disease incidence and nasopharyngeal carriage data are required to clarify this issue.

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Regulation and characterization of IL-17A expression in patients with chronic rhinosinusitis and its relationship with eosinophilic inflammation

To the Editor:

IL-17A is a proinflammatory cytokine synthesized by T_H17 cells.[1] Although several reports have demonstrated that IL-17A expression levels in sputum and lung tissue correlated with the severity of asthma symptoms, it remains unclear as to whether IL-17A is involved in the pathogenesis of severe chronic upper airway diseases, including chronic rhinosinusitis with nasal polyps (CRSwNPs).[2,3] We investigated the local production and regulation of IL-17A in nasal polyps (NPs) by using a recently developed *ex vivo* system.[4] In addition, local expression of IL-17A was compared among various chronic rhinosinusitis (CRS) phenotypes, and the role of IL-17A in the pathogenesis of CRS was discussed. Details on the methods are available in the Methods section of this article's Online Repository at www.jacionline.org.

Staphylococcus aureus enterotoxin B (SEB) is involved in the pathogenesis of CRSwNPs.[5] SEB stimulation of dispersed nasal polyp cells (DNPCs) induced significant IL-17A synthesis (Fig 1, *A*), suggesting that SEB exerts its pathogenic effects in patients with CRSwNPs through induction of IL-17A synthesis. Neutralization with IL-10 or IL-18 did not affect the SEB-induced IL-17A synthesis. In contrast, neutralization with IL-12/IL-23 p40 partially, albeit significantly, suppressed this synthesis. IFN-γ neutralization significantly improved IL-17A synthesis (Fig 1, *B*). These results suggest that production of IL-17A is positively and negatively regulated by p40 and IFN-γ, respectively.

The COX pathway also plays important roles in the pathogenesis of CRSwNPs.[4] Treatment with diclofenac caused a significant decrease in IL-17A production (Fig 1, *A*). Conversely, SEB-induced IL-17A production in diclofenac-treated DNPCs was enhanced by 21.6%, 45.8%, and 38.8% in the presence of prostaglandin (PG) E_2 administered at 10^{-8}, 10^{-7}, and 10^{-6} mol/L, respectively, when compared with control buffer treatment ($P = .001$). PGE_2, 10^{-7} and 10^{-6} mol/L, significantly increased IL-17A production compared with 10^{-8} mol/L PGE_2, indicating that the effect of PGE_2 was dose dependent, and the highest enhancement was achieved at 10^{-7} mol/L (Fig 1, *C*). This result suggests that COX metabolism, especially PGE_2, displays a proinflammatory role during SEB-induced IL-17A production. The inhibition by p40 neutralization was also seen in the presence of diclofenac ($P = .028$), suggesting the additive inhibitory activity by COX inhibition and p40 neutralization.

Correspondence

Age- and serotype-dependent antibody response to pneumococcal polysaccharides

To the Editor:

Although it is widely believed that infants younger than 2 years do not mount adequate responses to pneumococcal polysaccharides, there is anecdotal evidence that infants younger than 2 years are able to mount significant serotype-specific antibody responses to unconjugated pneumococcal polysaccharides. In a recent Letter to the Editor, Balloch et al[1] substantiated that 12-month-old children can mount adequate anti-polysaccharide antibody responses to vaccination with 23-valent pneumococcal polysaccharide vaccine.

The data obtained by Balloch et al[1] also revealed marked differences in serotype-specific immune responses in young children. Some serotypes (eg, 14, 19F, and 23F) elicited no significant antibody response, whereas other serotypes (eg, 2, 3, 8) elicited a high antibody response. Similar differences in immunogenicity between serotypes in young children have previously been reported.[2]

Serotypes 3 and 14 can be considered 2 extremes of a spectrum with respect to age- and serotype-dependent antibody responses to pneumococcal polysaccharides. In the study of Balloch et al,[1] in young children the highest postvaccination antibody concentration was found for serotype 3 (13.74 μg/mL), whereas the lowest postvaccination antibody concentration (and a nonsignificant response) was found for serotype 14 (0.41 μg/mL).[3] The opposite has been found in the elderly. In a recent study in elderly persons (>58 years old) in which antibodies to 14 serotypes were measured, the highest postvaccination antibody concentration was found for serotype 14 (19.76 μg/mL), whereas the lowest postvaccination antibody concentration was found for serotype 3 (1.19 μg/mL).[3] Thus children aged 1 year are unable to mount specific antibodies to serotype 14,[1,2] whereas elderly persons mount particularly high antibody responses to serotype 14 after vaccination with a 23-valent pneumococcal vaccine.[3-5] For serotype 14, Sorensen et al[6] also noted a pattern of increase according to age, with a very low mean fold increase in children but a sharply higher mean fold increase in adolescents and adults. In addition, children at age 1 year mount high specific antibody responses to serotype 3, whereas elderly persons mount weak antibody responses to serotype 3.[3,4] For serotype 3, lower postvaccination antibody levels have also been found in adults than in children.[7] Moreover, we found that even very young children were able to mount antibodies to serotype 3. In two 6-month-old children the postvaccination (Pneumovax; Merck & Co, Whitehouse Station, NJ) antibody concentrations to serotype 3 were 1.97 μg/mL and 2.3 μg/mL, respectively.

Taken together, Balloch et al[1] demonstrated that young children are able to mount anti-polysaccharide antibody responses to most pneumococcal serotypes. Their data further underscore the notion that the antibody response to pneumococcal polysaccharides is markedly age and serotype dependent. Some serotypes (eg, serotype 3) elicit high antibody responses in young children but not in elderly persons, whereas other serotypes (eg, serotype 14) elicit high antibody responses in elderly persons but not in young children. This strongly suggests that the regulation of the anti-polysaccharide immune response is serotype dependent. Further research is needed to unravel the nature of the regulatory systems.

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